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Estrogens and Endometrial Carcinoma

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A group of 205 women with endometrial carcinoma was matched for age, parity, and year of operation with a group of 205 women who had had hysterectomies for benign disease. In the former group, 32 patients had used conjugated estrogens, while in the latter group 12 had used this hormone, yielding a relative risk of 3.1 (P = 0.0008). Users of other forms of systemic estrogens showed similar elevations in relative risk. Relative risk was related to duration of use, progressing from no evidence of risk among those using the hormone for less than 5 years to an 11.5-fold greater risk for those using it for 10 years or more. Risk was also related to the strength of the medication. The relative risk for users of the 1.25-mg tablets was 12.7 as compared to a two- to fourfold greater risk among users of lesser strength tablets.

RECENT STUDIES indicate a significant increase, after years of relative stability, in the incidence rates for endometrial carcinoma, particularly on the West Coast of the United States. Much of the increase has occurred since 1969.[1,2] Other population-based studies indicate a modest increase over a 21-year period, 1953–1955 vs 1971–1973.[3] The largest systematic population-based survey found no increase in 1947–1948 versus 1969–1970.[4]

Three very recent reports noted an increased risk for endometrial cancer among users of exogenous estrogens, notably conjugated estrogens.[1,5,6]

This study of the patients in a single physician's practice compares the prior usage of exogenous estrogens of 205 endometrial cancer patients with that of 205 matched controls who were free of endometrial cancer at the time of hysterectomy.

MATERIALS AND METHODS

The study group consisted of 205 consecutive patients with endometrial carcinoma, excluding carcinoma *in situ*, seen in one private practice between 1947 and 1976. The records for each patient were examined and the age of the patient, her year of operation, her parity, and weight at diagnosis were abstracted. One control was chosen for each case from among those patients who had had a hysterectomy for a benign condition performed in the same year in which the patient with carcinoma was diagnosed. Once the year was determined, the specific match was chosen from all those available on the basis of being matched as closely as possible to the case on the bases of age and parity. If there were still a number of potential controls to choose from, the one whose weight was closest to that of the study case was chosen.

Once the study and control groups were identified, their records were reviewed, and information concerning hormone therapy, blood pressure, history of diabetes, history of abnormal uterine bleeding, and evidence of an atrophic vagina on clinical exam or cytologic smear was abstracted. A woman had to have used an estrogen-containing medication for at least 3 months to be designated a user, and use just prior to diagnosis to control abnormal bleeding was not counted.

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The measure of strength of an association used in these analyses is the relative risk (RR) as approximated by the relative odds.[7] The RR is a measure of the risk of disease among those having a particular exposure compared to those not exposed. An RR of 1.0 would indicate no difference in risk between those exposed and those unexposed. An RR of 2.0 would indicate that the exposed patients had a risk of the disease which was twice that for those not exposed. When the analyses were controlled for the influence of other variables, the estimate of RR was the maximum likelihood estimate obtained after stratification of the data on various levels of the control variable.[8] Exact 95% confidence intervals (CI) were calculated for the estimates of RR.[8,9] When the 95% CI does not include 1.0, the RR is statistically significant at the $P < .05$ level.

RESULTS

On the average, the patients with endometrial cancer were 56.5 years old and had 1.5 children. This compared with the corresponding values for the control group of 56.0 years and 1.6 children, which reflected the closeness of the age and parity matching. The average weight was greater for the study patients (148.3 lb) than the controls (141.0 lb). This difference was statistically significant ($P < 0.01$) and due primarily to the over representation of cases at the very high values (10.8% of the study patients weighed more than 180 lb versus 2.7% of the controls) rather than a shift of the entire distribution. Since an attempt was made to match by weight after year, age, and parity had been matched, these differences in weight are minimal estimates, and the true difference is probably greater.

The average diastolic blood pressure was nearly identical for study patients and controls (84.6 versus 84.0 mmHg), but systolic blood pressure was significantly greater for study patients than controls (146.6 versus 141.5 mmHg, $P < 0.05$). Among the 116 study patients and 133 controls for whom specific information was available, 8 study patients and 1 control gave a history of diabetes, yielding an RR of the disease among diabetics of 9.8 (95% CI = 1.1–369.4).

Fifty-five of the 205 patients with cancer and 31 of the 205 controls had used some form of estrogen-containing medication (RR = 2.1, 95% CI = 1.2–3.5). The majority had used conjugated estrogens (Table 1) yielding an RR of 3.1 (95% CI = 1.5–6.8) for this form of the drug. As seen in Table 1, all categories of systemic estrogens were associated with elevated RRs including intramuscular estrone and other types of estrogen tablets—primarily stilbestrol and ethinyl estradiol. Grouping all systemic estrogens yields an RR of 2.6 (1.5–4.6, 95% CI). There was no evidence of increased risk associated with vaginal estrogenic preparations (creams, estrogen-impregnated pressaries) or oral contraceptives, although the latter were not used frequently enough to be evaluated adequately. Matched pairs analysis yielded identical results (the RR for systemic estrogens = 2.5).

The effects of length of use and strength of tablet usually used were investigated for those using conjugated estrogens. The RR increased with increasing duration of use (Table 2), with no appreciable increase in risk apparent for those using the medication for less than 5 years. Those using it for 5 to 9 years had a fourfold increase in risk, and those using it for 10 years or more had a risk 11½ times that of nonusers. Those usually using the 1.25-tablet had a risk markedly above that for users of the 0.3- or 0.625-mg tablets (Table 3). The estimate of RR was lower for users of the 0.6-mg tablet than for those using the 0.3-mg dose, but the estimates were variable because of the small numbers involved. When attention was restricted to those using the drug for more than 5 years, the RR for users of the 0.3-mg tablet was identical to that for those using the 0.625-mg tablet. The associations with duration of use and strength of tablet do not confound each other, as the estimates of RR in Tables 2 and 3 remained unchanged when control for the other variable was added.

As noted, the anticipated differences between study patients and controls in obesity, hypertension, and history of diabetes were present. None of the patients with a history of diabetes were estrogen users. Control for weight and systolic blood pressure did not diminish the associations with hormone use. In fact, simultaneous control for both of these variables increased the RR for systemic estrogens to 3.6 (1.9–6.8, 95% CI).

For 184 of the study patients and 179 of the controls there was clear and specific information recorded on whether there had been any abnormal uterine bleeding in the year prior to hysterectomy. As anticipated, the study group had a positive history much more frequently than the controls (85 versus 33%). The relative risk for use of systemic estrogens was slightly higher

TABLE 1. ENDOMETRIAL CANCER CASES AND CONTROLS AND RELATIVE RISKS* ACCORDING TO TYPE OF HORMONE THERAPY RECEIVED

Hormone therapy	*Study group*	*Control group*	*Relative risk*	*95% Confidence intervals*
None	150	174	1.0	
Conjugated estrogens	32	12	3.1	1.5– 6.8
Other oral estrogens	5	2	2.9	0.5–30.8
Oral "hormones" NOS†	8	6	1.5	0.5– 5.5
Intramuscular estrogens	6	3	2.3	0.5–14.5
Oral contraceptives	1	3	0.4	0.0– 4.9
Vaginal estrogen preparations	3	5	0.7	0.1– 3.6

* Relative to a risk of 1.0 for those having received no hormones
† NOS = not otherwise specified

TABLE 2. ENDOMETRIAL CANCER CASES AND CONTROLS AND RELATIVE RISKS* ACCORDING TO YEARS OF USE OF CONJUGATED ESTROGENS (UNKNOWNS EXCLUDED)

	Years of use		
	0–4	5–9	10+
Study group	8	7	10
Control group	8	2	1
Relative risk	1.2	4.1	11.6
95% Confidence interval	0.4–3.5	0.8–28.4	1.5–242.7

* Relative to a risk of 1.0 for those having received no hormones

TABLE 3. ENDOMETRIAL CANCER CASES AND CONTROLS AND RELATIVE RISKS* ACCORDING TO STRENGTH OF CONJUGATED ESTROGEN TABLET USUALLY USED (UNKNOWNS EXCLUDED)

	Strength (mg)		
	0.3	0.625	1.25
Study group	7	14	11
Control group	2	9	1
Relative risk	4.1	1.8	12.7
95% Confidence interval	0.8–40.5	0.7–4.9	1.8–552.3

* Relative to a risk of 1.0 for those having received no hormones

among those with no history of abnormal bleeding than it was for those with such a history (3.4 versus 1.8). However, with the numbers involved these two estimates were not significantly different from each other.

Most endometrial cancers had been carefully staged* and graded (Table 4). The percent distribution by stage was remarkably similar for users and nonusers of systemic estrogens. There was some evidence of a difference in pathologic grading between users and nonusers, there being a higher proportion of users in the lowest grade and a lesser proportion in the highest. However, the differences were not statistically significant, and there was no evidence of a linear trend in the differences between the users and nonusers (χ^2 for linear trend = 1.16, $P > 0.2$).

DISCUSSION

The recent studies reporting a high incidence of endometrial cancer among users of conjugated estrogens have been criticized on a number of grounds.[10,11] These have included questions concerning the accuracy of the pathologic diagnoses, the appropriateness of controls who either have had other gynecologic cancers or who have not had hysterectomy, the adequacy of control for other relevant factors, and the possible interrelations between hormone use, uterine bleeding, and aggressive workup of postmenopausal uterine bleeding. The controls in this series were drawn from patients who had had hysterectomy for benign conditions in the same gynecologist's practice from which the cases were drawn. The uteri of the control patients were all subjected to pathologic examination and found to be free of malignancy. Information on the major known risk factors for endometrial cancer (age, parity, weight, blood pressure, and history of diabetes) was present for most of the study patients and controls, making it possible to control for these factors when assessing the influence of exogenous hormones. In addition, the control group included a sufficient number of patients with abnormal uterine bleeding in the year prior to hysterectomy to allow us to control for this variable. In the face of all these differences, we found an association with use of conjugated estrogens which was similar to that in the previous reports.[1,5,6]

Two other associations are noteworthy, in that they concern issues to which the other studies could not speak or which they could address only superficially because of small numbers of observations. First, the excess risk appears to apply to systemic estrogens of all kinds (intramuscular estrone, stilbestrol, ethinyl estradiol), not just conjugated estrogens. Second, there appears to be a positive dose–response relation between risk of the malignancy and both duration of use and strength of the medication taken. Perhaps particularly important is the absence of any evidence of excess risk among those using the smaller doses for less than 5 years. One can never prove the absence of an associa-

TABLE 4. NUMBER AND PERCENT DISTRIBUTION BY STAGE AND GRADE OF THE TUMOR FOR ENDOMETRIAL CANCER PATIENTS WHO USED SYSTEMIC ESTROGENS AND THOSE WHO DID NOT (UNKNOWNS EXCLUDED)

	Users		Nonusers	
	Number	Percent	Number	Percent
Stage*				
Ia	30	61	88	59
Ib	10	20	23	15
Ic	6	12	20	13
II	1	2	5	3
III & IV	2	4	13	9
Grade†				
1	31	63	80	54
2	10	20	37	25
3	4	8	10	7
4	4	8	20	14

* χ^2 (5 df) for the difference in distribution of the users and nonusers = 2.23 ($P > 0.8$).

† χ^2 (3 df) for the difference in distribution of the users and nonusers = 1.84 ($P > 0.5$).

* Staging according to FIGO with exception that Stage Ia is carcinoma of the endometrium with invasion limited to the endometrial stroma (carcinoma *in situ* was not included), Stage Ib indicates myometrial invasion up to one-third of the thickness of the myometrium, and Stage Ic indicates invasion beyond one-third of the myometrium, but not penetrating the serosa.

tion, and with some of the numbers involved these findings should be considered cautiously. But perhaps this observation can point the way to further studies which will help with the risk-benefit decisions that must be made concerning these drugs.

Several aspects of this private practice should be kept in mind when evaluating these results. The study patients and controls represent a mixture of 2 groups of patients, those routinely seen by the author and those referred to him because of the problem that eventually led to the patients' hysterectomies. The proportions of each may vary between study and control patients. In addition, the referral patterns for those with endometrial cancer could be different from those with benign disease. The extent to which these factors could influence the results is unknown, but it should be noted that, in this practice, estrogens have always been used with care in women who had an intact uterus. Fifty-five percent of the women in this practice who received estrogens had had hysterectomy and oophorectomy previously. Among those with intact uteri, the smaller dosage (0.3 mg) was usually prescribed when warranted.

That systemic estrogens are associated with excess risk of uterine cancer should not be surprising. Gynecologists through the years have been concerned with the effects of estrogens in müllerian tissues and have been aware that estrogens may either initiate or promote growth of tumors of the uterus. Forty years ago, Novak[12] warned of the carcinogenic possibilities of estrogenic substances. A few papers have reported cases which associate exogenous estrogens with endometrial carcinoma.[13-15]

Endometrial carcinoma has been reported concurrently with estrogen-secreting tumors of the ovary[16,17] and among patients with the Stein-Leventhal syndrome.[18] Indeed, increased conversion of androstenedione to estrone, present in this syndrome, has been suggested as a factor among women in general who develop this tumor.[19,20]

More recently, nonsteriodal estrogens have been linked to adenosquamous carcinoma of the endometrium in patients with gonadal dysgenesis,[21] to vaginal and cervical adenocarcinoma in young women exposed during fetal life,[22] and perhaps to endometrial cancer among breast cancer patients undergoing hormone therapy.[23] In addition, one report indicated a possible excess of endometrial carcinoma among women taking sequential oral contraceptives.[24]

On the other hand, the appearance of endometrial carcinoma in patients with a prior bilateral oophorectomy has been documented,[25-27] although a few of these patients had received estrogenic hormones.[26] In addition, in one series, 54% of patients with endometrial cancer (and 50% of the controls) had atrophic vaginal changes.[28] In the current study, 64.8% of patients never on hormone therapy had evidence of atrophic vaginas on vaginal smear.

While much publicity has surrounded the findings concerning estrogen drugs and endometrial cancer, it should be noted that in most series the actual percentage of all endometrial cancers due to these drugs is quite small. Even if all of the excess risk associated with the use of systemic estrogens is presumed to be due to a causal association, only 31 of the 205 cases in this series could then be attributed to this source. We are obviously as much in the dark about the major etiologies of this disease as we are for most malignancies.

However, cancer of the breast and endometrium remain matters of great concern for those patients receiving estrogens. The RR of breast cancer among estrogen users was recently found to approximate that for nonusers for about the first 12 years following onset of therapy.[29] Thereafter, the RR increased to about twofold after 15 years. Further study is required to assess the significance of the elevated risk in the long follow-up intervals.

The established or possible risks associated with the use of this medication must be balanced against its benefits. Not all menopausal women have symptoms, nor do all benefit from estrogen therapy. A significant proportion of women maintain an estrogenic effect in the vaginal smear for years after the menopause. Others with apparent estrogen deficiency simply have insufficient symptoms for treatment. On the other hand, perhaps as many as half of the women in the menopause have appreciable symptoms which include hot flashes, nervousness, joint and bone symptoms (osteoporosis and arthralgia), atrophic vaginitis with dyspareunia, cystourethritis, as well as other problems. Many of these symptoms may be alleviated dramatically by estrogenic therapy.

Two other factors need to be considered in this weighing of risks and benefits. It has been estimated that in the near future 50% of women in the postmenopausal age range will have had a hysterectomy and therefore no longer be at risk for this disease.[30] In addition, the high cure rate of this cancer indicates that the impact of estrogens on the duration of life is certainly much less than its impact on the occurrence of endometrial cancer. While the lifetime risk of development of this disease is 2.2% for whites and 1.1% for blacks,[31] follow-up data indicate a 70.9% 5-year and a 55.8% 10-year survival rate.[3] With early diagnosis, the cure rate may well approach 95%.[32]

These data should provide some information on which decisions involving the use of systemic estrogens

can be made. Additional studies involving larger numbers of women are necessary to further refine the risk data.

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